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Key Differences in Pulmonary and Extrapulmonary NEC Management

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Boehringer Ingelheim Pharmaceuticals, Inc. Here's your host, Dr. Alexandria May.

Dr. May:
This is *Project Oncology* on ReachMD, and I'm Dr. Alexandria May. Today I'm speaking with Dr. Lowell Anthony about the distinctions between pulmonary and extrapulmonary neuroendocrine carcinomas, or NECs for short, and what recent discussions from the European Neuroendocrine Tumor Society, more commonly referred to as ENETS, may mean for clinical practice.

Dr. Anthony is the Chief of the Division of Medical Oncology and Co-Director of the Radiopharmaceutical Therapy Program at the University of Kentucky Markey Cancer Center in Lexington. Dr. Anthony, thanks for being here today.

Dr. Anthony:
It's a real pleasure, Dr. May.

Dr. May:
So I'd like to start with an overview. Pulmonary NEC, particularly small cell lung cancer, has long been the reference point for aggressive neuroendocrine disease. But recent discussions, like those highlighted in ENETS forums, suggest that extrapulmonary NEC may represent a distinct clinical entity, despite sharing high-grade morphologic features.

From your perspective, Dr. Anthony, where do the meaningful biological and clinical differences begin, and why does that distinction matter when it comes to management?

Dr. Anthony:
A lot has happened in understanding neuroendocrine tumors, neuroendocrine neoplasms, and neuroendocrine carcinomas over the last decade. The most important distinction between the different types of neuroendocrine neoplasms really comes down to morphology. When the pathologist says it's a poorly differentiated carcinoma or neuroendocrine carcinoma, that establishes the setting for what the best treatment's going to be. So that's really the first evidence that we have that we're not dealing with an indolent process that we see with neuroendocrine tumors.

The complexity is that some neuroendocrine tumors are high grade, but all neuroendocrine carcinomas are high grade. So this becomes very confusing to not only the patients when you try to explain it to them, but also the physicians.

Dr. May:
Accurate classification is where everything else hinges, but it's also where things can break down in practice. With that being said, what pathologic and clinical criteria should guide the distinction between poorly differentiated NEC and other high-grade neuroendocrine neoplasms? And where does getting that classification right most directly influence management?

Dr. Anthony:
There are several key aspects of understanding this area of biology. It really comes down to if a pathologist talks about necrosis—we know we're dealing with a high-grade neoplasm. The Ki-67 index can be helpful in neuroendocrine tumors when we have Grade 3, which may have a Ki-67 index above 20. It does not help much in classification of the neuroendocrine carcinomas, which are all poorly differentiated and completely different from even the high-grade neuroendocrine tumors that may have a Ki-67 of 40, 50 or 60 percent. So it's different biology.

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Dr. May:
Now, presentation patterns also seem to differ depending on the site of origin. So how do pulmonary and extrapulmonary NECs typically present, and how should site of origin shape the diagnostic workup, including imaging choices and whether evaluations like brain staging carry the same weight outside of small cell lung cancer?

Dr. Anthony:
So when patients with small cell lung cancer present, they typically have a tobacco history. We think of this as being tobacco-linked. Patients may present with a wide variety of symptoms; it may be involuntary weight loss, chest pain, or shortness of breath, and it could just be incidentally on a screening CT scan. But more often, the small cell is going to metastasize fairly early in the history. So we would want to stage with a head CT and get a total body CT scan from the very beginning because of the high incidence of brain metastases with pulmonary small cell.

Now, as we contrast that to extrapulmonary neuroendocrine carcinomas, there, the symptoms will reflect potentially which organ may be the primary site. And we're usually dealing with a large mass where the primary may be in the pancreas or in the colon. And there, the symptoms may be bleeding, pain, involuntary weight loss, nausea, or vomiting, and be distinctive. So the staging would be a total body CT, but may not include a head CT. But that'd be individualized more if these tumors are not going to have the same incidence of brain metastases. But in some individuals, there may be an indication to get CNS staging.

Dr. May:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Lowell Anthony about how clinicians can navigate the similarities and differences between pulmonary and extrapulmonary neuroendocrine carcinomas.

Now, Dr. Anthony, first-line treatment for many patients still draws heavily from pulmonary NEC paradigm, but how well does that translate across extrapulmonary sites? And are there situations where the evidence suggests we should be thinking differently?

Dr. Anthony:
Because of the sheer number of patients and their research data that we can use in the small cell lung model, if we apply that to extrapulmonary, it's really not one-for-one. There is some overlap. For instance, in those patients who may have RB1 loss or p53 mutation a platinum doublet may very well be the primary treatment, which the NCCN guidelines certainly support.

However, the use of durvalumab or atezolizumab as we would in small cell is not that supported. So we really need more research to know if we should add immunotherapy to extrapulmonary small cell like we do in small cell. So even though there's similarities in the biology, there's really distinct differences that really relate to the organ of origin.

One of the differences between pulmonary neuroendocrine carcinomas and extrapulmonary carcinomas is the sensitivity to oxaliplatin. We think about the FOLFOX area regimen as being potentially active in extrapulmonary neuroendocrine carcinomas, whereas within the small cell pulmonary, we don't even consider an oxaliplatin-based regimen as part of it, even in the refractory setting. So that's one of the key differences that the practitioner will focus on early on—to think about a platinum doublet versus an oxaliplatin-containing regimen.

Dr. May:
Now, DLL3 has also been a recurring theme in recent ENETS discussions. Originally characterized in small cell lung cancer, it's now being reported across several extrapulmonary NECs as well. What do those findings suggest about the shared biology across NEC subtypes, and how should clinicians be thinking about DLL3 right now?

Dr. Anthony:
DLL3 is a downstream marker of ASCL1, which is part of the Notch pathway. So this is one of the commonalities that extrapulmonary neuroendocrine carcinomas have with pulmonary. We see a high frequency of incidence of DLL3 expression—somewhere probably around 70 or 80 percent—in extrapulmonary neuroendocrine carcinomas. So this has become a critical target for research.

Data that Dr. Jaume Capdevila talked about at ENETS were some of the very first data where the group took this targeted agent BiTE—a bispecific targeted T-cell engager, obrixtamig—that links the CD3 with the DLL3 engager with chemotherapy. This has been most interesting—the early data that's being shown at ENETS—where there was a 75 percent overall response rate with a median progression-free survival of 7.7 months. So this is a really good start of how we can improve patient outcomes by combining the standard right now, a platinum doublet, with this particular BiTE molecule.

Dr. May:
Before we wrap up here, Dr. Anthony, what practical takeaways should clinicians keep in mind when evaluating or managing patients

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with NEC?

Dr. Anthony:
First of all, know what you're treating. I'd ideally talk to the pathologist. Review your scans with a radiologist. Understand, is it pulmonary? Is it extrapulmonary? If it's extrapulmonary, is it colon? Is it prostate? Is it pancreatic? It could even be endometrial or GYN.

We know that there's first-line treatment with platinum doublets for most of these, but for the patients who may become refractory to the platinum doublet, we need to start thinking of the second line early. So the message I want to leave people with today is, start planning what you do during or at the beginning of management, such as checking a DLL3 level or a tissue expression IHC if possible, because it may have research implications later on.

What Dr. Capdevila presented is certainly not ready for primetime, but we want to encourage more research. People are thinking that there is hope that we've got a new potential biomarker here, and outcomes are being impacted. And as we look at regimens that are active in second-line therapy, they could become more active in the first line, like Dr. Capdevila presented. It's a small step forward, but in a rare subset of neuroendocrine carcinoma, it's really a step in the right direction.

Dr. May:
With those final thoughts in mind, I want to thank my guest, Dr. Lowell Anthony, for sharing his insights on distinguishing pulmonary from extrapulmonary neuroendocrine carcinoma and incorporating the latest ENETS updates into clinical practice.

Dr. Anthony, it was great having you on the program.

Dr. Anthony:
Thank you, Dr. May.

Announcer:
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